FABP4 predicts atherogenic dyslipidemia development. The PREDIMED study

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ABSTRACT

Objective: Atherogenic dyslipidemia (AD), characterized by high plasma triglycerides and low HDL particles, is considered one of the main effectors of vascular damage associated with obesity, metabolic syndrome (MS) and type 2 diabetes. Adipocyte fatty acid-binding protein (FABP4) plasma concentrations have been linked to metabolic alterations that are associated with adiposity. The aim of the present study was to prospectively analyze the predictive value of baseline FABP4 plasma concentrations for the development of AD.

Methods: In the frame of the PREDIMED study, a multicenter dietary interventional trial, we prospectively measured the baseline plasma FABP4 levels and AD incidence over a six-year follow-up period (median 4 [IQR, 3–5 years]) in 578 volunteers who visited their general practitioners because of their cardiovascular risk factors.

Results: During follow-up, 103 participants developed AD. Baseline plasma FABP4 levels were associated with new onset AD over the follow-up period (OR 1.03 [95% IC: 1.00–1.05], p = 0.020). This increased risk was observed in women but not in men. Among women, those in the highest tertile of FABP4 had a 2.54-fold increased relative risk of developing AD compared to the lowest tertile (HR 2.54 [95% CI, 1.31–4.93], p for trend = 0.008).

Conclusions: Elevated plasma FABP4 concentrations should be considered as a potential marker of metabolic derangement, which may predict the development of AD in women.

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1. Introduction

The combination of high plasma triglycerides (TG) and low HDL concentrations is referred to as atherogenic dyslipidemia (AD), a main lipid alteration observed in metabolic diseases, such as abdominal obesity, metabolic syndrome (MS) and type 2 diabetes (T2D) [1]. AD partially accounts for the residual cardiovascular risk (CVR) observed after hypercholesterolemia treatment with statins in high cardiovascular risk patients and is considered one of the main effectors of vascular damage in these metabolic diseases [2].

AD is also characterized by the presence of an increased number of small and dense LDL particles and TG-rich lipoprotein remnants, increased ApoB and non-HDL cholesterol concentrations. Larger VLDL, smaller HDL and generally prolonged postprandial hyperlipidemia are also present.

The pathogenic basis of AD is not fully established, although insulin resistance (IR) is considered to play an important role in its development. Alterations in insulin action increase the adipocyte lipolytic activity of hormone sensitive lipase (HSL), which increases non-esterified fatty acid (NEFA) secretion [1]. When NEFAs reach the liver, they may mainly contribute to the formation of diacylglycerol (DAG) and TG rather than going to oxidative pathways. DAG accumulation accounts for an increased IR state and TG formation, leading to synthesis and secretion of large TG-rich VLDL particles [3], which leads to the formation of smaller and denser forms of both LDL and HDL particles. Alternatively, Apo A1 dissociates from the small HDL, and it is rapidly cleared from plasma through the kidney, contributing to low HDL concentrations [4]. IR is associated with decreased LPL activity, also increasing TG-rich lipoprotein plasma concentrations [5].

The strong association of AD with obesity suggests that adipose tissue-derived molecules could be involved in the process. Among these, the adipocyte fatty acid-binding protein (FABP4)
must be taken into account. FABP4 is a small cytoplasmic lipid chaperone that has an important role in the trafficking of fatty acids in subcellular compartments. FABP4 knock-out animal models show reduced lipolysis and are protected from the development of hyperinsulinemia, hyperglycemia, IR and atherosclerosis [6–8]. FABP4 seems to be implicated in adipocyte lipolysis control by a direct interaction with HSL [9].

Circulating FABP4 levels are increased in obese subjects compared to lean subjects [10]. Several metabolic pathologies linked to altered adipose tissue dysfunction, such as MS, T2D, human immunodeficiency virus-associated lipodystrophy, polycystic ovary syndrome and non-alcoholic steatohepatitis, also show enhanced serum FABP4 levels [11–14]. Plasma FABP4 levels have been suggested to be a predictor of MS [15], T2D [16] and subclinical atherosclerosis development in women [17]. In a cross-sectional assessment, our group reported that FABP4 was strongly correlated with AD in T2D patients [18]. In the present study, we evaluated the hypothesis that plasma FABP4 levels could predict the development of AD.

2. Methods

2.1. Study population

This study has been conducted within the PREDIMED trial (http://www.predimed.es, http://www.predimed.org) which design has been reported in detail previously [19,21]. The PREDIMED (PREvención con Dieta MEDiterránea) study is a multicenter, parallel group, randomized and controlled clinical trial being conducted in Spain that aims to assess the effects of two Mediterranean diets, one supplemented with either extra virgin olive oil or mixed nuts versus a low-fat control diet, on the primary prevention of cardiovascular diseases among persons with high CVR [19,20]. This is a nested study conducted within one of the centers of the PREDIMED trial (Reus node) including the first 578 participants randomized in this node that had undergone at least 1-year of follow-up at the moment of analysis.

The participants studied were community-dwelling men (aged 55–80 years) and women (aged 60–80 years) without previously documented cardiovascular disease. They were recruited on the basis of having T2D or 3 or more of the following CVR factors: hypertension, hypertriglyceridemia (serum TG ≥ 1.69 mmol/l or requiring treatment), low plasma HDL-cholesterol levels (<1.03 mmol/l in men or <1.29 mmol/l in women), overweight or obesity (BMI > 25 kg/m²), current smoking habit, or family history of premature coronary heart disease.

Incident (new-onset) AD was defined as low HDL-cholesterol (<1.03 mmol/l in men or <1.29 mmol/l in women) associated with elevated TG (≥1.69 mmol/l) at any time during the follow-up assessment. National Cholesterol Education Program’s Adult Treatment Panel III criteria were used to define MS [22].

All participants provided informed consent, and the protocol was approved by the institutional review boards.

2.2. Clinical measurements

At baseline, lifestyle variables, medical conditions and medication use were recorded.

Trained personnel measured weight, height, waist circumference and blood pressure as previously described [20]. All examinations were repeated and medical condition and medication use were revised yearly during the follow-up.

2.3. Biochemical determinations

Laboratory technicians were blinded to the intervention. Plasma glucose, serum cholesterol, HDL-cholesterol and TG levels were measured yearly during the follow-up using standard enzymatic automated methods. LDL-cholesterol was estimated by the Friedewald equation.

The plasma FABP4 levels and fasting insulin at baseline were determined with commercial ELISA kits (Bio Vendor Laboratory Medicine Inc., Brno, Czech Republic and Linco Research, St. Charles, MO, USA). The antibodies used in the human FABP4 ELISA were highly specific for human FABP4, with no detectable cross-reactivity to human FABP1, FABP2, FABP3 or FABP5. The intra- and inter-assay coefficients of variation were 5.3 and 3.9%, respectively (FABP4) and 6.0 and 10.3%, respectively (insulin).

All biochemical determinations were performed at fasting state.

2.4. Statistical analyses

Continuous variables are presented as the mean (standard deviation, SD) for normally distributed data, as the median [interquartile range, IQR] for non-normally distributed data, and as frequencies (n) or percentages (%) for categorical variables. Data with skewed distributions, as determined with the Kolmogorov–Smirnov test, were log-transformed before analysis.

An unpaired Student’s t-test and a χ² test were used to compare the mean of the quantitative variables or frequency of qualitative traits between non-AD-incident and AD-incident participants.

Partial correlation analyses were done to study the relationship between baseline plasma FABP4 concentrations, the lipid profile and anthropometric parameters, adjusting for age and sex.

A longitudinal analysis was conducted (exposure: baseline FABP4; outcome: AD incidence) to evaluate the relationship between FABP4 plasma concentrations and AD incidence. Unadjusted and adjusted logistic regression models were fitted. In adjusted models, we included as potential confounders age, waist circumference, TG, and HDL-cholesterol (all continuous), intervention group (2 dummy variables), and baseline hyperlipidemic and oral antidiabetic treatment (dichotomous) and waist circumference changes during the follow-up.

Participants without AD at baseline were categorized into sex-adjusted tertiles of baseline FABP4 concentrations. Cox regression models were fitted to assess the relative risk of AD across FABP4 tertiles, estimated with hazard ratios (HR) and 95% confidence intervals (CI). The time variable was the interval between baseline measurement date and the date of the last follow-up, death or outcome diagnosis, whichever occurred first. Participants who were free of outcomes or lost during follow-up were censored at the date of the last visit. The assumption of proportional hazards was tested using time-dependent covariates.

Three Cox regression models were fitted: an unadjusted model; a model adjusted for age, waist circumference and intervention group (Model 1); a model adjusted for age, waist circumference, TG, HDL-cholesterol, intervention group, and hypolipidemic and oral antidiabetic treatment at baseline (Model 2), and a model adjusted for age, waist circumference, TG, HDL-cholesterol, intervention group, and hypolipidemic and oral antidiabetic treatment at baseline and waist circumference changes during the follow-up (Model 3). The lowest tertile baseline FABP4 level was used as the reference group.

FABP4 by sex interaction was tested using a product term (2 degrees of freedom) in the Cox regression (Model 3) with all the main variables already included in the model. The p-value of the
likelihood ratio test for this product term was used to assess effect modification by sex.

Kaplan–Meier survival curves were plotted to estimate the probability of remaining free of the outcome during the follow-up for women by baseline FABP4 plasma tertiles. The model was adjusted for age, waist circumference, TG, HDL-cholesterol, intervention group, and hyperlipidemic and oral antidiabetic treatment at baseline and waist circumference changes during of the follow-up.

Two-tailed p-values < 0.05 were considered significant. Statistical analyses were done with the SPSS (version 17.0, SPSS Inc., Chicago, IL).

3. Results

The mean age of the participants at baseline was 67 (6) years, and the study included 259 men and 319 women. Women showed significantly higher baseline FABP4 plasma concentrations than men (34.4 [26.9–42.4] μg/l vs. 18.6 [15.1–23.6] μg/l; p < 0.001) (Table 1). After adjustment for age and gender, positive correlations were observed at baseline between FABP4 and total body weight (r = 0.318; p < 0.001), BMI (r = 0.356; p < 0.001), waist circumference (r = 0.29; p < 0.001) and TG (r = 0.18; p < 0.001). In non-T2D participants, after adjusting for age and gender, the baseline plasma FABP4 levels were positively correlated with baseline insulin levels (r = 0.135; p = 0.02).

Among the 578 participants studied, 519 did not meet the AD criteria at baseline. Over the 6-year study period, with a median follow-up of 4.0 (3.0–5.0) years, a total of 103 (35 men and 68 women) out of 519 participants developed new-onset AD. Women who developed incident AD had significantly higher FABP4 levels at baseline compared to women who did not develop AD (36.5 [27.8–48.8] μg/l vs. 33.1 [26.3–41.2] μg/l, p = 0.007) (Table 1). The cumulative incidence of AD was not significantly different among the dietary intervention groups (17.2 [11.8–22.6] % for the Mediterranean diet enriched with virgin olive oil group, 20.6 [14.9–26.4] % for the Mediterranean diet enriched with nuts group, and 22.2 [15.4–29.0] % for the low-fat control diet group; p = 0.496). General characteristics of AD-free participants at baseline by later AD case status are summarized in Table 1. Participants who developed AD had significantly higher baseline BMI, plasma TG and insulin levels and lower HDL-cholesterol concentrations compared to those who did not develop AD.

Table 2 shows the results of the logistic regression analyses. FABP4 was associated with AD incidence in the whole group. However, this association was only statistically significant in women. In women, the unadjusted model revealed that having an increase of 1 unit in the baseline plasma FABP4 concentrations accounted for a 3.0% relatively higher risk of developing AD, even after adjusting for potential confounders (OR 1.04 [95% CI 1.01–1.06], p = 0.006). In non-diabetic women (n = 155), the model remained significant after adjusting for baseline insulin (OR 1.04 [95% CI 1.00–1.08], p = 0.034). The predictive value of FABP4, for women, in multivariate Model 2 was validated by comparing ROC curves from models including or excluding FABP4.

Table 3 shows the results of the Cox proportional hazard models with the outcome of AD and the FABP4 plasma concentration categorized in tertiles as the main exposure. There was not a significant interaction by sex (p = 0.398) Women in the highest tertile of FABP4 had a significantly higher risk of developing AD compared to the lowest tertile, even after adjusting for age, baseline waist circumference, TG and HDL-cholesterol, intervention group and hyperlipidemic and oral antidiabetic treatment at baseline and waist circumference changes during of the follow-up (HR 2.54 [95% CI 1.31–4.93], p for trend = 0.008).

Women with circulating FABP4 levels in the highest tertile had significantly lower AD-free survival compared to those in the lowest tertile (p = 0.006) (Fig. 1).

Among the 578 participants studied, 226 did not meet the MS criteria at baseline. Over the 6-year study period, a total of 128 out of 226 participants developed new-onset MS (only 18% due to DA feature). Participants who developed incident MS had significantly higher FABP4 levels at baseline compared to participants who did not develop MS (26.9 [17.6–35.3] μg/l vs. 21.7 [16.3–30.1] μg/l, p = 0.037). An increase of 1 unit in the baseline plasma FABP4 concentrations accounted for a 3.0% relatively higher risk of developing MS (OR 1.03 [95% CI 1.02–1.06], p = 0.045) in an unadjusted model. However, statistical significance was lost after adjusting for potential confounders (Model 2) (OR 1.01 [95% CI 0.98–1.05], p = 0.522).

Finally, over the 6-year follow-up, plasma FABP4 concentrations were not associated with the risk of incidence of T2D in the 303 non-T2D subjects at baseline from the 578 participants included in the present study.

4. Discussion

In this study, we demonstrated for the first time that elevated FABP4 plasma concentrations in women were associated with an increased risk of developing AD after a median follow-up of 4.0 years. We have already reported that FABP4 and AD were strongly associated in a cross-sectional study conducted on T2D patients. In that study, the inverse association between adiponectin and the direct association with FABP4 were most strongly associated with hypertriglyceridemia and low HDL-cholesterol [18]. Moreover, in that study, we showed that the impact on lipid metabolism was independent of insulin levels, suggesting a direct effect of FABP4 on lipid metabolism. Now that we have been able to show that elevated FABP4 levels preceded the lipid metabolism...
### Table 1
Baseline characteristics of the 578 participants.

|                          | All | Non-AD at baseline | p
|--------------------------|-----|--------------------|---
| **Participants, n**      | 578 | 416                | 103 |
| **Age, years**           | 67.4 (5.8) | 67.4 (5.7) | 67.0 (6.1) | 0.475 |
| **Women, %**             | 55.2 | 50.7               | 66.0 | 0.005 |
| **BMI, kg/m²**           | 29.5 (3.3) | 29.5 (3.3) | 30.1 (3.3) | 0.014 |
| **Waist circumference, cm** | 100.7 (8.5) | 100.2 (8.5) | 101.4 (8.8) | 0.330 |
| **In men**               | 102.6 (7.9) | 102.5 (7.7) | 104.7 (8.4) | 0.124 |
| **In women**             | 99.2 (8.7) | 98.6 (8.9) | 99.8 (8.3) | 0.351 |
| **Non-HDL-cholesterol, mmol/l** | 4.0 (0.9) | 3.9 (0.9)   | 4.0 (0.9)  | 0.492 |
| **HDL-cholesterol, mmol/l** | 1.3 [1.1–1.5] | 1.4 [1.2–1.6] | 1.1 [1.0–1.2] | <0.001 |
| **Men**                  | 18.6 [15.1–23.6] | 18.3 [15.0–23.7] | 19.4 [16.1–23.7] | 0.288 |
| **Women**                | 34.4 [26.9–42.4] | 33.1 [26.3–41.2] | 36.5 [27.8–48.8] | 0.007 |
| **Fasting glucose, mmol/l** | 6.4 (2.0) | 6.2 (1.8) | 6.5 (2.1) | 0.173 |
| **Fasting insulin, pmol/l** | 33.3 [23.6–50.7] | 31.9 [21.5–49.3] | 36.8 [28.5–50.7] | 0.026 |
| **Physical activity, kcal/day** | 283 (264) | 301 (265) | 262 (287) | 0.182 |
| **Type 2 diabetes prevalence,** | 47.6 | 45.0 | 47.6 | 0.632 |
| **Fibates medication,** % | 3.5 | 1.9 | 6.8 | 0.008 |
| **Statins medication,** % | 40.7 | 40.4 | 48.5 | 0.133 |
| **Hypolipidemic treatment,** % | 45.2 | 43.0 | 56.3 | 0.015 |
| **Hypertensive treatment,** % | 76.1 | 75.2 | 76.7 | 0.758 |
| **Oral antidiabetic treatment,** % | 32.0 | 28.6 | 36.9 | 0.101 |

AD, atherogenic dyslipidemia; FABP4, adipocyte fatty acid binding protein. Data are given as the mean (SD) or median [interquartile range], unless otherwise indicated.

1. Unpaired Student's t-tests and χ² tests were used to compare the mean of quantitative variables or the frequency of qualitative traits between non-AD and AD-incident participants.

2. Log-transformed before analysis.

3. Non-type 2 Diabetes: n = 298 in all participants; n = 227 in non-AD incident sub-group and n = 51 in AD incident sub-group.

### Table 2
Risk of incident atherogenic dyslipidemia (odds ratio and 95% confidence intervals).

<table>
<thead>
<tr>
<th></th>
<th>All non-AD participants n = 519</th>
<th>Men n = 240</th>
<th>Women n = 279</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted model</strong></td>
<td>1.03 (1.02–1.05)</td>
<td>1.02 (0.98–1.06)</td>
<td>1.03 (1.01–1.05)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>0.371</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td>1.03 (1.01–1.05)</td>
<td>1.01 (0.97–1.05)</td>
<td>1.03 (1.01–1.05)</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td>1.03 (1.00–1.05)</td>
<td>1.01 (0.96–1.07)</td>
<td>1.03 (1.01–1.06)</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td>1.03 (1.00–1.05)</td>
<td>1.00 (0.96–1.06)</td>
<td>1.04 (1.01–1.06)</td>
</tr>
<tr>
<td><strong>FABP4, µg/l</strong></td>
<td>40.7</td>
<td>40.4</td>
<td>48.5</td>
</tr>
<tr>
<td><strong>Hypolipidemic treatment,</strong> %</td>
<td>45.2</td>
<td>43.0</td>
<td>56.3</td>
</tr>
<tr>
<td><strong>Hypertensive treatment,</strong> %</td>
<td>76.1</td>
<td>75.2</td>
<td>76.7</td>
</tr>
<tr>
<td><strong>Oral antidiabetic treatment,</strong> %</td>
<td>32.0</td>
<td>28.6</td>
<td>36.9</td>
</tr>
</tbody>
</table>

AD, atherogenic dyslipidemia; OR, odd ratio; CI, confidence interval. Logistic regression models with outcome of AD onset and the main exposure of plasma baseline FABP4 concentrations. Even after adjusting for baseline insulin: among all subjects (n = 278), OR 1.06 (1.03–1.09); p = <0.001; among men (n = 123), OR 1.03 (0.96–1.11), p = 0.426; and among women (n = 155), OR 1.04 (1.00–1.08) = 0.034.

4. Adjusted for age, baseline waist circumference and intervention group.

5. Adjusted for age, baseline waist circumference, triglycerides and HDL-cholesterol, intervention group, hypolipidemic and oral antidiabetic treatment at baseline.

6. Model 2 plus waist circumference changes during the follow-up. In all models with all non-AD participants, the model was also adjusted for sex.

### Table 3
Hazard ratios (95% confidence intervals) for atherogenic dyslipidemia across tertiles of plasma FABP4 concentrations.

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td>n = 77</td>
<td>n = 82</td>
<td>n = 81</td>
<td></td>
</tr>
<tr>
<td><strong>FABP4, µg/l</strong></td>
<td>&lt;16.2</td>
<td>16.2–21.7</td>
<td>&gt;21.8</td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted model</strong></td>
<td>1 [Reference]</td>
<td>1.48 (0.65–3.38)</td>
<td>1.13 (0.47–2.72)</td>
<td>0.791</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td>1 [Reference]</td>
<td>1.43 (0.61–3.31)</td>
<td>1.00 (0.39–2.54)</td>
<td>0.997</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td>1 [Reference]</td>
<td>1.14 (0.45–2.93)</td>
<td>0.70 (0.26–1.89)</td>
<td>0.454</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td>1 [Reference]</td>
<td>1.05 (0.41–2.64)</td>
<td>0.66 (0.25–1.79)</td>
<td>0.402</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>n = 94</td>
<td>n = 96</td>
<td>n = 89</td>
<td></td>
</tr>
<tr>
<td><strong>FABP4, µg/l</strong></td>
<td>&lt;28.8</td>
<td>28.9–39.7</td>
<td>&gt;40.1</td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted model</strong></td>
<td>1 [Reference]</td>
<td>1.08 (0.57–2.06)</td>
<td>2.00 (1.12–3.58)</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td>1 [Reference]</td>
<td>1.07 (0.56–2.05)</td>
<td>1.98 (1.09–3.61)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td>1 [Reference]</td>
<td>1.34 (0.69–2.63)</td>
<td>2.31 (1.22–4.38)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td>1 [Reference]</td>
<td>1.40 (0.70–2.78)</td>
<td>2.54 (1.31–4.93)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

FABP4 indicates adipocyte fatty acid binding protein. Cox regression models with outcomes of AD onset and the main exposure of FABP4 tertiles.

4. Adjusted for age, baseline waist circumference and intervention group.

5. Adjusted for age, baseline waist circumference, triglycerides and HDL-cholesterol, intervention group, hypolipidemic and oral antidiabetic treatment at baseline.

6. Model 2 plus waist circumference changes during the follow-up.
disturbance, our hypothesis is reinforced. In the present study, we have extended the evaluation of the association between AD and FABP4 by conducting a prospective study. A significant association between baseline FABP4 levels and AD development was observed throughout the entire group; however, when we analyzed the results separately for men and women, only the association among women reached statistical significance. Each unit of baseline FABP4 levels was associated with 3% increased risk of developing AD in women. The non-significant relation between FABP4 and AD in men might be at least partly, by a low statistical power probably due to the fact that women had double incidence of AD than men. Women in the third FABP4 tertile had a 2.54-fold higher hazard risk of developing this lipid metabolism disturbance after adjustment for potential confounding variables. The difference in plasma FABP4 concentrations between men and women has been clearly established by our group and others [10,11]. FABP4 is expressed in higher quantities in subcutaneous adipose tissue than in visceral fat [23]. Women accumulate fat in the subcutaneous adipose tissue, while men tend to store fat in the visceral fat compartment. This fact may account for the differences in FABP4 concentrations. If FABP4 had a direct effect on lipid metabolism, then the higher concentrations in women would explain the impact observed on AD development according to sex.

The results of the multivariate analysis support that the association between baseline FABP4 levels and AD development is likely to be independent of insulin action. Moreover, this association resulted to be independent of adiposity indices. In fact, neither BMI nor waist circumference were predictors of AD development in logistic regression analysis, and the predictive value of FABP4 was maintained both in obese and non-obese subgroup of participants (data not shown). In other words, FABP4 was not just a marker of IR or obesity in its association with AD. Our data support the idea of a direct impact of FABP4 on lipid metabolism. Previous studies have shown that FABP4 interacts with HSL, facilitating lipolysis in the adipose tissue [9]. Because an increase in the adipocyte lipolytic activity has been considered to be the initial process of AD, FABP4 could be implicated in this metabolic situation. Although this study was performed in the context of a diet intervention project, the observed impact of FABP4 on lipid metabolism alterations seems to be independent of the diet group, because the association between FABP4 and AD remained after adjusting by dietetic intervention group. In addition, the number of patients developing AD was equally distributed among the three diet regimes.

Our results are in line with previous studies in Asian populations that show that plasma FABP4 levels were able to predict the development of both MS and T2D in studies with longer follow-up periods (5 and 10 years, respectively) [15,16]. However, in our study, no association was observed between baseline FABP4 plasma concentrations and the risk of incident MS or T2D. Differences in sample size, gender distribution, incidences and baseline characteristics of population could explain the discrepancies.

There are some limitations to our study. First, the Mediterranean cohort studied was older in age and at high risk for cardiovascular disease. The generalization of our findings to younger and/or healthier participants from other geographical locations is uncertain. Because this is an association study, we cannot establish causality, although we could establish an adequate temporal sequence, and the robustness of the associations after multiple adjustments allows us to infer a direct role of FABP4 on lipid metabolism beyond its potential as a biomarker reasonably free of confounding. Another important limitation of our study is that it was conducted in a cohort that was undergoing nutritional interventions, which may have had differential effects on the incidence of AD. However, to address this limitation and minimize its effects, we have adjusted all the analyses for the intervention group throughout the follow-up.

5. Conclusion

In conclusion, FABP4 is a clear marker of participants who are prone to profound metabolic alterations and are, therefore, participants who need closer medical control for the reduction of metabolic and vascular risks. To implement FABP4 measurements in clinical practice to design personalized preventive strategies, the predictability of this molecule must be re-evaluated in other populations.

Conflict of interest

A.C., N.B., I.L., M.B., A.G.-A. and L.M have nothing to disclose. The Fundación Patrimonio Comunal Olivarero and Hobiñablanca (Málaga, Spain), California Walnut Commission (Sacramento, CA), Borges and Morella Nuts (Reus, Spain) donated the olive oil, walnuts, almonds and hazelnuts, respectively, used in the PREDIMED study. None of the funding sources played a role in the design, collection, analysis or interpretation of the data or in the decision to submit the manuscript for publication.

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